Vol. 66, No. 4 Established 1884 April 1949

# ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

## DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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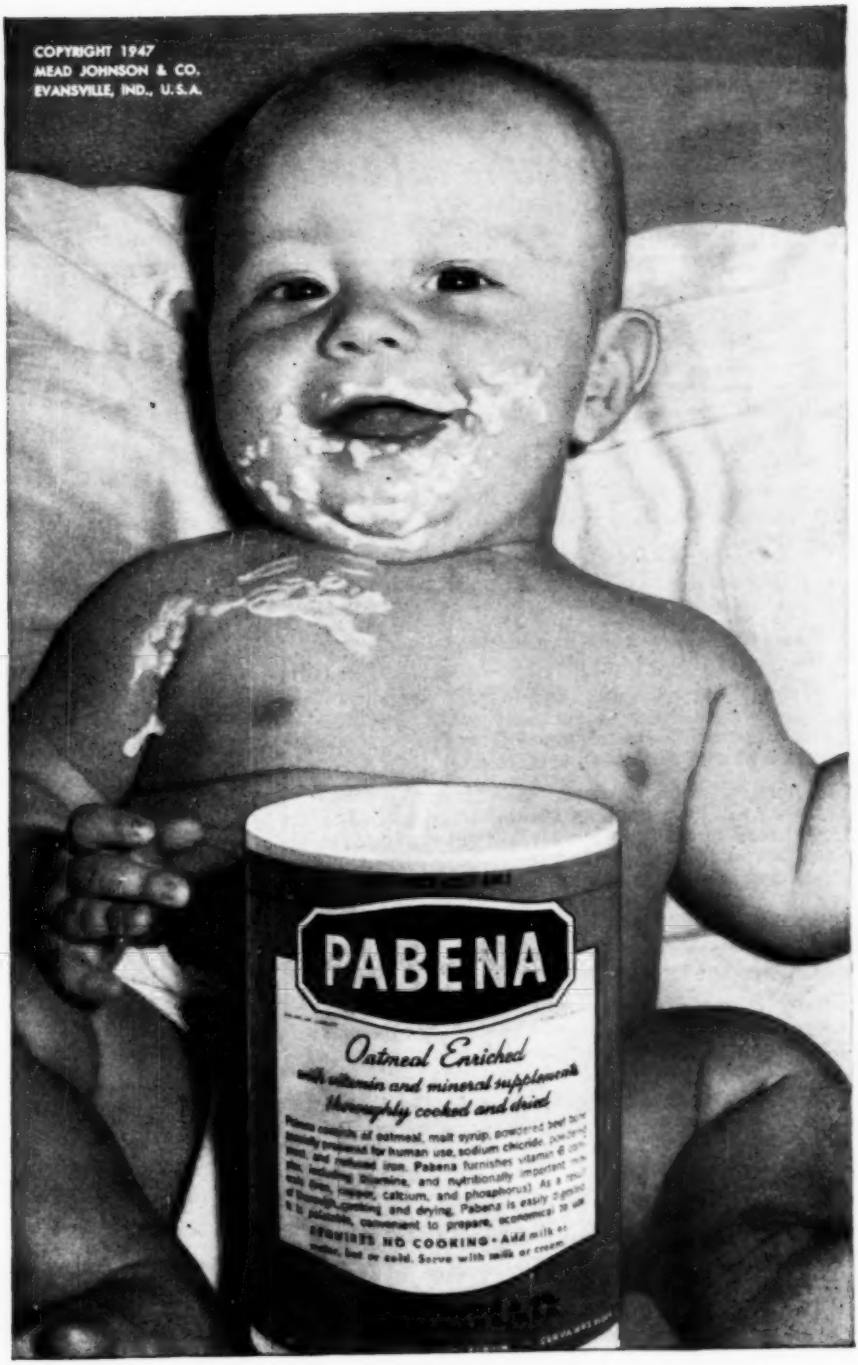
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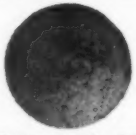
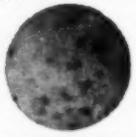


Film of Mennen Baby Oil (0.21 mm), 20,000 X. *Note homogeneous character.*



Film of evaporated baby lotion (0.21 mm), 20,000 X. *Note breaks, irregularity.*

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1. Elsner, H.—A Method for the Study of the Penetrability of Liquid and Semisolid Films Used in Skin Protection. Journal of Investigative Dermatology. Vol. 10, No. 4, April 1948. *Reprints upon request.*

2. Schwartz, L., Mason, H.S., and Albritton, H.R.—A Method for the Evaluation of Protective Ointments. Occupational Medicine 1:376-385 (April) 1946.

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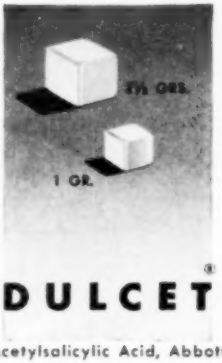


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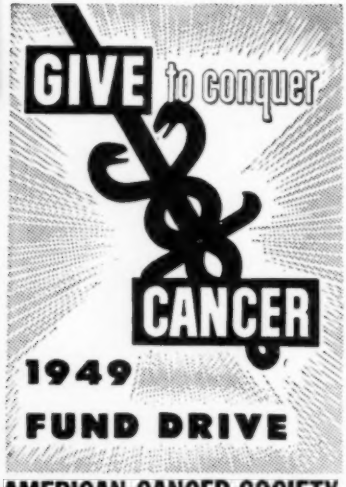


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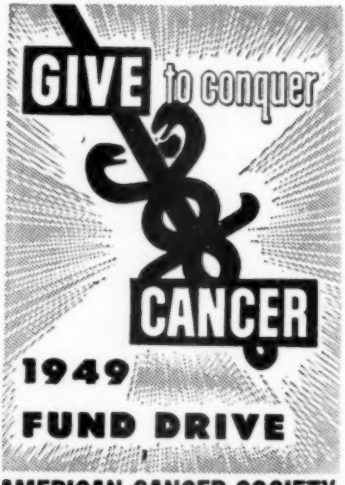


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(1) Frisk, A. R., et al: Brit. Med. J. 1:7, 1947; (2) Ledbetter, J. H., and Cronheim, G. E.: Am. J. Med. Sci. 216:27, 1948.

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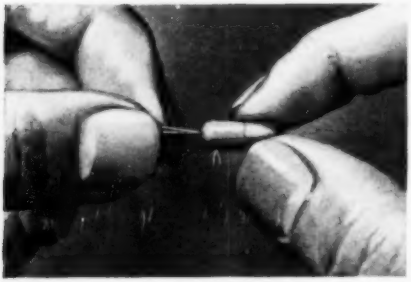

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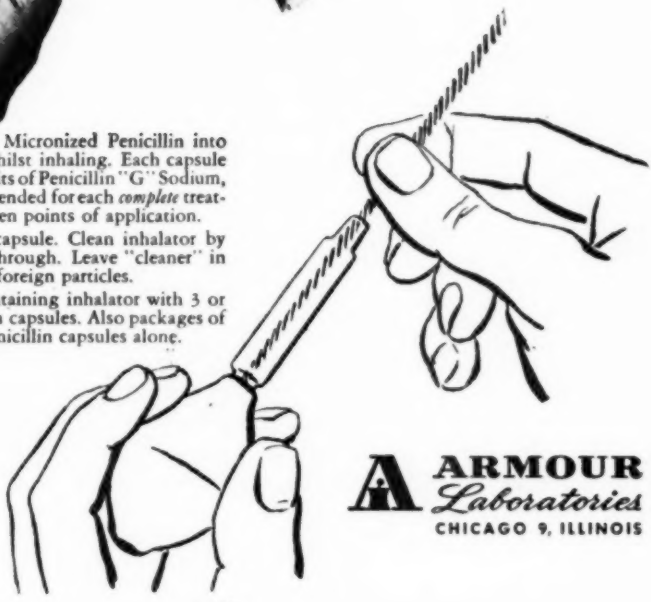

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VOL. 66 APRIL 1949 No. 4

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# METHEMOGLOBINEMIA*

## A CAUSE OF CYANOSIS IN INFANTS AND CHILDREN

GEORGE W. WALLIKER, M.D.
Portland, Oregon.
AND
E. H. BAXTER, M.D.
Columbus, Ohio.

Methemoglobinemia is by no means an uncommon occurrence in infants and children. It should be emphasized that this alarming condition can rapidly lead to death unless the etiology of the cyanosis is suspected. Death due to methemoglobinemia per se is largely inexcusable because of the simplicity and specificity of the treatment.

It was first reported in 1886 when Rayner, quoted by Leader,[1] described 17 cases of methemoglobinemia with the sudden appearance of cyanosis in infants traced to diapers and pads freshly stamped with ink containing nitrobenzene. Accidental poisoning with industrial and medicinal compounds and the continued use of obsolete drugs account for the majority of the cases today. Occasionally, it may be due to sepsis.

Methemoglobin may result from the ingestion, inhalation, or absorption through the skin[2] of the following substances: potassium chlorate, bismuth subnitrate, sulfonamides, particularly sulfanilamide and sulfapyridine, antigas ointment,[3] crayons,[4] well water containing nitrates, aniline, nitrobenzene, acetanilide, aminophenols, antipyrin, ferricyanides, shoe dyes, perfumery, artificial

*From the Department of Pediatrics, College of Medicine, Ohio State University and The Columbus Children's Hospital.

flavorings, acetophenacetin, plasmochin, phenylhydrazine, sulfonal, pyrogallic acid and methylene blue. Cases of familial idiopathic methemoglobinemia have been reported.[5] The production of enterogenous methemoglobinemia due to nitrite-forming bacilli has been suggested[6] and disputed.[7]

The striking feature of this condition, particularly in children and infants, is the extreme cyanosis. These small patients cannot describe the sensations of burning and tingling, headache, vertigo and visual disturbances which are concomitant symptoms of methemoglobin intoxication. Therefore, the diagnosis must be made from the objective symptoms.

Methemoglobinemia is most commonly confused with congenital heart conditions, respiratory diseases, cardiac arrhythmias and intracranial injuries. Generally, the diagnosis is not made until the cyanosis fails to disappear under oxygen therapy, or the characteristic chocolate color of the blood is noted in the course of some laboratory procedure.

We wish to discuss five cases of methemoglobinemia due to varied causes, their mechanism of production and treatment.

## CASE REPORTS

*Case* 1. P. M. B., a white girl, aged 6 weeks, entered The Children's Hospital on November 4, 1945. Birth had been normal, and the birth weight was 5 pounds 9¾ ounces. The past history was not unusual, except for a brief period of "diarrhea" immediately after birth which had apparently ceased spontaneously. Two days prior to admission a physician prescribed a pink liquid for a rash on the infant's tongue. On the following day the infant refused her formula and vomited once. She became lethargic but cried out occasionally "as if in pain." On the morning of admission the infant had a peculiar "bluish-yellow" color. The urine was very dark in appearance. Physical examination showed a poorly nourished, deeply cyanotic, infant girl whose skin was bluish-yellow in appearance and whose sclerae were icteric. The lips were cyanotic. The rectal temperature was 102.6° F. The lung fields seemed to be clear. The heart rate was 160 per minute, and there was a questionable murmur. The heart was normal in size, and no arrhythmias were detected. The navel showed evidence of subsiding infection. The liver and spleen were both

palpable 2 cm. below the costal margins. There was a generalized lymphadenopathy. It was thought that the infant had a severe anemia with jaundice due to infection. The infant was given continuous oxygen by tent. Penicillin therapy was immediately instituted.

The cyanosis was not affected by oxygen. Because of the obvious severe anemia, blood withdrawn from the femoral vein for gross examination and cross-matching was chocolate colored. Within thirty minutes all the cells were disintegrated leaving a translucent, brownish fluid. A hemoglobin determination at this time was 6.0 Gm. per cent. There were 1,840,000 red cells per cu. mm. An icterus index could not be done because the blood hemolyzed spontaneously. A blood culture was negative after eight days' incubation. Because of the history of the stomatitis, for which a pink medicine was given, methemoglobinemia due to potassium chlorate poisoning was suspected. The infant was transfused with 35 cc. of whole blood. Eight hours after admission methylene blue (1.5 mg. per kilogram of body weight) was given intravenously and followed by 35 cc. of whole blood. The infant's progress was steadily downward, and the infant expired twelve hours after admission. Autopsy permission was refused. It was later determined that the infant had received 30-35 grains of potassium chlorate over a period of two and one-half days. Death was due to intoxication with this drug resulting in a severe methemoglobinemia and fulminating hemolytic anemia.

*Case 2.* M. W. J., a white infant girl, aged 13 days, was admitted to The Children's Hospital on December 23, 1946. Seven other siblings were normal. The infant had been a full term baby, normally delivered, and her neonatal history had been uneventful until the day of admission. She lived on a farm where the powdered milk formula was prepared with boiled well water. At 11:00 A.M. on the day of admission the infant suddenly developed cyanosis which became intensified with crying. The infant was placed in continuous oxygen immediately. Physical examination revealed a well developed, well nourished, 10-pound infant girl crying lustily and appearing well except for a profound cyanosis of the entire body which was accentuated in the nail beds and mucous membranes. Rectal temperature was 101° F., pulse rate was 180 per minute, and respirations were 30

per minute. Continuous oxygen therapy seemed to lessen the cyanosis only slightly, and crying, either in or out of oxygen, accentuated the condition. The chest was clear to auscultation. The liver was palpable 3 cm. below the right costal margin. The spleen was not felt. Methemoglobinemia was suspected and corroborated by the chocolate-brown color of the withdrawn blood. The hemoglobin was 13.9 Gm. per cent. Upon shaking, no change in the appearance of the blood was noted, and a comparison with the blood of another infant revealed a dissimilarity in color.

The infant was given 5 mg. of methlene blue intravenously (1 mg. per kilogram of body weight). In thirty minutes some improvement was apparent in the color of the infant, and an additional 2.5 mg. (0.5 mg. per kilogram of body weight) were administered with further improvement in appearance. One-half hour after the second injection blood withdrawn from the femoral vein seemed to have a "normally red" appearance. The hemoglobin determination at this time was 15.1 Gm. per cent. The urinalysis was negative. The cyanosis had disappeared completely by the following morning. The infant was discharged on the third hospital day. No spectroscopic or spectrophotometric methods were available at this time for quantitative analysis for methemoglobin so that the degree of methemoglobinemia was not known. However, a solution of blood gave an absorption band in the region of 600-650 mu when examined in the spectrophotometer which was not present in normal blood. The well water used in the preparation of the formulae given to this infant revealed the presence of nitrates in the amount of 60 parts per million.

*Case 3.* L. T., a white infant girl, aged 2 months, was referred to The Children's Hospital by the family physician twelve hours after the sudden onset of severe cyanosis. On the day prior to admission the infant became pale and irritable and began to refuse feedings. The birth history was normal. After one month of breast feeding the infant was changed to a powdered milk formula prepared with water obtained from a limestone well on the grandparents' farm. Physical examination revealed a well developed, well nourished infant girl with a rectal temperature of 100.2° F. There was a generalized "heliotrope" cyanosis of the body which was accentuated in the nail beds, finger tips, toes, lips, and several excoriated areas about the buttocks. Respirations were 85 per

minute, and a severe tachycardia was present. After the child had been in oxygen a short time, it was noted that the conjunctival mucosae appeared pale. The chest was clear, but evidence of air hunger was characterized by the gasping respirations. No cardiac murmurs could be heard, and the heart was not enlarged to percussion. The liver was soft and palpable 3.5 cm. below the right costal margin. The tip of the spleen was felt. At this time a methemoglobin determination* revealed 5.05 Gm. per cent and a total hemoglobin concentration of 8.5 Gm. per cent.

The infant was given methylene blue intravenously (1.5 mg. per kilogram of body weight) and was returned to the oxygen tent. Thirty minutes later only slight improvement was noted in the color. One and one-half hours after the initial injection, an additional 0.5 mg. per kilogram of body weight of methylene blue was administered intravenously. One-half hour later methemoglobin concentration was 43 per cent (methemoglobin—4.6 Gm. per cent, hemoglobin—10.7 Gm. per cent). Seven and one-half hours after the initial dose of methylene blue, the methemoglobin had fallen to 3.1 Gm. per cent, and the total hemoglobin was 11.9 Gm. per cent. At seventeen and one-half hours the methemoglobin was 0.8 Gm. per cent, and the total hemoglobin was 12.3 Gm. per cent. The infant was normal in color. She had been given 40 mg. of methylene blue and 100 mg. of ascorbic acid orally in this interval. The liver had receded 2.5 cm. Respiratory and cardiac rates were normal. Analysis of the parents' well water containing a brown sediment and thus considered to be "polluted" revealed 0.08 parts per million of nitrates. The water from the grandparents' well was clear and thought to be more potable. It had a nitrate content of 90 parts per million.

*Case* 4. Girl M., a colored premature infant, weighing 4 pounds 2½ ounces, was born by precipitate delivery. The infant's mother was severely ill at the time from an undiagnosed disease. At operation following delivery, the mother was found to have a ruptured appendix. She subsequently succumbed and at autopsy was found to have peritonitis, pelvic abscesses, and caseous abdominal lymph nodes. The infant was admitted to The Children's

*Methemoglobin determinations were done by a spectrophotometric modification of the method of Evelyn and Malloy using a Coleman spectrophotometer. (See J. Biol. Chem., 126: 665, Dec. 1938).

Hospital on the seventeenth day of life because of failure to do well since birth. Physical examination revealed a normally developed, dehydrated, colored infant appearing acutely and chronically ill. The conjuctivae and buccal membranes were extremely pale, and the infant's hemoglobin was estimated to be about 4.0 Gm. per cent. The chest was apparently clear, and the heart tones were described as being of good quality. There were no cardiac murmurs. The liver and spleen were not palpable. Blood withdrawn from the infant for cross-matching was almost black in color, but upon dilution with saline it was found to be chocolate colored. The diagnosis of methemoglobinemia was made, and a determination spectrophotometrically revealed the presence of practically 100 per cent methemoglobin. Total hemoglobin was 11.6 Gm. per cent. The infant was given 2 mg. of methylene blue per kilogram of body weight intravenously. At the time of the injection, in spite of her naturally dark color, there was cyanosis of the palms, lips and nail beds. The methylene blue was followed by a transfusion of 30 cc. of whole blood. A search for possible agents which might have caused the methemoglobinemia was unsuccessful, and it was thought that sepsis was the most likely possibility. A blood culture revealed the presence of a small gram-negative rod which could not be successfully isolated due to a heavy overgrowth of B. subtilis. A stool culture was negative. The infant was given methylene blue and ascorbic acid orally. Blood withdrawn one hour following the injection of methylene blue was found to contain 4.47 Gm. per cent of methemoglobin and 13.2 Gm. per cent of total hemoglobin. A determination on the morning following admission disclosed 4.45 Gm. per cent methemoglobin and 13.6 Gm. per cent total hemoglobin. Another transfusion of 30 cc. of whole blood was given, and oral methylene blue was continued. The infant was kept in oxygen. She was given 3 cc. of 5 per cent sodium sulfadiazine twice daily by oral route. On the second hospital day the methemoglobin concentration was 2.4 Gm. per cent, and the total hemoglobin was 15.0 Gm. per cent. The Mazzini test was negative. A blood sulfadiazine level on the seventh hospital day was 24.1 mg. per cent. On the eighth hospital day the serum protein was found to be 4.88 per cent, and the infant was given 25 cc. of pooled plasma intravenously without difficulty. One and one-half hours later the

infant was found dead in her crib. A postmortem blood culture failed to grow any organisms after nineteen days' incubation. Postmortem methemoglobin determination was 0.73 Gm. per cent, and the total hemoglobin was 17.9 Gm. per cent. The autopsy findings were compatible with sepsis.

*Case* 5. E. R., a white boy, aged 2½ years, had been well until the day of admission. Three hours before admission he ate an undetermined number of enteric coated tablets which he found on a neighbor's trash pile. Later he refused his lunch and complained of feeling ill. His mother noticed that he was pale and that his lips were blue. He began to complain of abdominal pain but did not vomit. At this time he was brought to the hospital. Physical examination showed a well-developed and nourished white boy who appeared to be acutely ill with a slate-like coloration of the skin and cyanosis of the lips, mucous membranes and nail beds. He was listless, complained of headache, and disliked sitting up. He was somewhat disoriented. The lungs were clear and respirations did not seem abnormal. The heart rate was 144 per minute and the rhythm regular. There were no murmurs. Blood pressure was 80/54.

The liver was palpable 1½ fingerbreadths below the right costal margin. It was soft and nontender. The spleen was not palpable. Neurological examination was normal. The diagnosis of acute drug intoxication with resultant methemoglobinemia was made, and it was suspected, and later confirmed by analysis, that the tablets were enteric-coated sodium nitrite. A blood sample was obtained, and the child was given 2.2 mg. of methylene blue intravenously per kilogram of body weight. The stomach was washed with normal saline. The material obtained was fluid and had the color of the enteric-coating substance on the tablets. No pieces of tablet were recovered. Four grams of sodium bicarbonate were placed in the stomach. The initial methemoglobin determination revealed 6.5 Gm. per cent and the total hemoglobin level, 12 Gm. per cent. Thirty-one minutes later the methemoglobin concentration had risen to 7.6 Gm. per cent, and the total hemoglobin was 9.45 Gm. per cent. The boy was given an additional one mg. per kilogram of body weight of methylene blue intravenously. Because of the low functional hemoglobin he was placed in an oxygen tent. Two hours following the second dose

of methylene blue examination of the blood revealed 5 Gm. per cent of methemoglobin and 10.5 per cent of total hemoglobin. Forty-five minutes later the cyanosis had largely disappeared. The boy was sitting up in bed and taking fluids by mouth. The pulse rate at this time was 140 per minute and was full and strong. By the following morning the boy was fully recovered.

## DISCUSSION

The death of the first patient was unquestionably due to intoxication by potassium chlorate with methemoglobinemia complicated by a fulminating hemolytic anemia. Potassium chlorate in repeated doses has a cumulative effect, since the chlorate ion is not destroyed in the body but is slowly excreted by the kidney. The drug was introduced as an oxidizing germicide, but it has been shown to have little action against bacteria.[8] Unfortunately, its use in the treatment of stomatitis has crept into textbooks.[9] Its use is to be condemned because more effective and less toxic agents are available. Gettler and St. George[10] reported a case of fatal poisoning in a 3-year-old boy for whom potassium chlorate was prescribed as a gargle over the telephone. The medication was mistakenly given orally with death in six hours after the appearance of cyanosis. At autopsy the blood was choclate brown in color and showed methemoglobin spectroscopically. Miller[11] reported an episode of cyanosis in a diabetic woman who had been given 12 grams of bismuth subnitrate over a forty-eight hour period for diarrhea. She was found to have 70 per cent methemoglobin upon admission to the hospital. A 3-week-old infant [12] was given 3 grams in buttermilk for diarrhea with cyanosis and death occurring in twelve hours. In 1907 Boehme[13] reported the case of an 18-month-old child who was given bismuth subnitrate by enema for an x-ray study. A cleansing enema was given following the procedure, but cyanosis due to methemoglobinemia developed and was followed by death. Four other cases[14, 15, 16] due to bismuth subnitrate have been found in the literature, the latest in 1947.[17] Poisoning has occurred from the use of ammonium nitrate as a diuretic.[18] Fortunately, the methemoglobin-forming sulfonamides are used less often today. Sulfanilamide is the worst offender. Hartmann and co-workers[18] followed the production of methemoglobin in infants and children who received sulfanilamide and concluded that while there was an excessive individual variation in the rate and degree of methe-

moglobin formation, in general, the dosage of sulfanilamide and its blood concentration seemed to have a direct relationship to the methemoglobinemia. Others[19] have failed to find any definite relationship between blood concentrations of sulfanilamide and sulfapyridine and the amount of methemoglobin produced. However, some degree of methemoglobinemia was observed in almost every infant who received either drug.

In February 1945, three premature infants and 32 newborn infants on the pediatric wards of the Louisville General Hospital[20] suddenly developed cyanosis. A careful search for the etiology of the outbreak failed until a nurse recalled that new, freshly stamped diapers had been used in the nurseries before laundering. A second episode occurred in the same hospital eight months later, this time due to unlaundered wash cloths stamped with ink containing aniline and used to wash the excoriated buttocks of three infants with diarrhea.

Stevenson and Forbes[21] reported a 12-month-old infant girl who had become poisoned by oil of mirbane (nitrobenzene) traced to an exterminator spray which had been used on her bed. A similar case report[22] involved 3-week-old twin siblings whose mattress had been sprayed with "Cresco," containing nitrobenzene. Levin[23] reports two cases of his own and 11 of Riviere's following the use of shoe dye on the shoes of infants and children between the ages of 8 months and 11 years.

Recent reports by Ferrant[24], Schwartz and Rector,[25] Comly,[26] and Faucett and Miller[27] concerned infants with methemoglobinemia traced to well water. In the United States, thus far, all reports have come from areas having wells drilled in sandstone or limestone, apparently allowing ready access to the water supply of surface nitrates by seepage through faults in the stone. It is not generally realized that formulae prepared from powdered milk diluted with well water contain three times as much water as do formulae prepared from diluted whole cow's milk. Therefore, the nitrate content of a powdered milk formula may be three times as great.

Recently, reports of idiopathic familial methemoglobinemia have appeared[5, 28]. Idiopathic methemoglobinemia has two characteristics which distinguish it from that of toxic origin. The

methemoglobin is not free in the plasma but is found only in the red cells, and, following exposure to air, it does not readily convert to hemoglobin as does the methemoglobin due to intoxication.[29] As a rule, the conversion of hemoglobin to methemoglobin resulting from toxic drugs occurs within the red cells, and the latter are not injured. High concentrations of certain methemoglobin-forming drugs, however, may result in actual destruction of the corpuscles. This is especially true of acetanilid, acetophenetidin, aniline, nitrobenzene, phenylhydrazine, pyrogallic acid, plasmochin and potassium chlorate. Goodman and Gilman state that "methemoglobin-containing cells apparently are more vulnerable to physiologic stress and to destruction by the reticulo-endothelial system. The result is the disintegration of erythrocytes."[30]

Renal function may be seriously impaired because of the precipitation of hemoglobin and methemoglobin in the renal tubules. Yuile et al.[31] readily produced a pathological lesion resembling "transfusion kidney" by the injection of hemoglobin into rabbits whose kidneys had previously been damaged by a short period of ischemia or by the use of a specific kidney poison, sodium tartrate. This damage was a consistent finding in the presence of acid urine in contrast to the lack of such disturbances when the urine was alkaline. It has been shown that the action of nitrites on blood is inhibited by ammonia.[32]

Darling and Roughton[33] believe that the mechanism of production of methemoglobin is due to the formation of compounds intermediate between reduced (ferrous) hemoglobin and oxidized (wholly ferric) methemoglobin. There are four ferrous atoms in the hemoglobin molecule, and the conversion of one or more atoms to "ferric" methemoglobin leads to an increased affinity of the remaining ferrous atoms for oxygen. Once hemoglobin is transformed to methemoglobin, oxygen is held tenaciously by the red cells and is not available for use by the tissues. It has also been shown that the dissociation curve of the remaining oxyhemoglobin is disturbed, thereby enhancing the anoxemia.[34] These factors thus help to explain the persistence of the cyanosis even after what is sometimes considered to be adequate therapy. It also explains the air hunger which is present in the more severely poisoned patients. Over a variable period of time a spontaneous reversible reaction occurs, and the methemoglobin is reconverted to hemo-

globin. Generally, only a fraction (20 per cent to 40 per cent) of the total hemoglobin is available for oxygen transportation to the tissues.

Cyanosis becomes clinically evident when the methemoglobin reaches a level of 3.0 Gm. per cent or 12.3 per cent of the total hemoglobin.[25] Rapid pulse, tachypnea and air hunger occur. Passive congestion of the viscera result from the ineffectual cardiac output associated with the tachycardia. The liver is generally palpable. A severe, underlying anemia is generally found clinically. Rapidly increasing jaundice may be present, especially with those drugs which, in addition, produce liver damage. Cardiac murmurs may be heard but are not common unless there is an associated hemolytic factor to the intoxication. The rapid heart rate and noisy respirations preclude the auscultation of a murmur in many cases.

In infants the cyanosis usually involves the entire body to varying degrees. Older children manifest the cyanosis by blueness of the lips, mucosae and nail beds. Their skin may often have a peculiar slate-gray appearance. If the process is a hemolytic one, oliguria is apt to occur. This may result from the toxic effect of the drug itself or from precipitation of free hemoglobin and methemoglobin in the kidney tubules. The urine should always be alkalinized in these patients as a precautionary measure. Low functional hemoglobin resulting in cerebral anoxia may produce convulsions.

Treatment of the methemoglobinemia should be instituted early in the course of the condition. A 1.0 per cent aqueous solution of methylene blue is given slowly by the intravenous route. The dosage is 1.5 to 3.0 mg. per kilogram of body weight. The drug may be diluted to any desired amount with normal saline. Several of the cases treated in this manner[16, 25] have shown a rather prompt disappearance of the cyanosis within 30 to 60 minutes. This rapid conversion of methemoglobin to hemoglobin has not been true in our experience, several hours being required for the conversion. In addition, with our later cases we have found that the oral administration of methylene blue in doses of 10 mg. every four to six hours is a useful adjunct. Orally, the drug is only one-tenth as effective as it is when used intravenously.

The mechanism of conversion of methemoglobin to hemoglobin

is believed by Hauschild[36] and Wendel[37] to be due to the reversible oxidation reduction or redox system of methylene blue and its colorless form. The latter, according to Wendel, is the effective agent. Colorless (reduced) methylene blue is thought to be produced in the red cells and more actively metabolizing tissues by the action of enzyme systems. The oxidizing action of greater doses of methylene blue is the rationale for the production of methemoglobin in the treatment of cyanide poisoning. Methylene blue is ineffective in the treatment of carbon monoxide poisoning, although it has been recommended and employed for this purpose.[38]

Thionine and ascorbic acid will cause the conversion of methemoglobin to hemoglobin by a redox system similar to methylene blue. Lian[5] and associates first used ascorbic acid for the treatment of familial methemoglobinemia. Hawley et al.[39] found that the addition of sodium bicarbonate enhanced the effect of ascorbic acid by inhibiting its excretion. Reports on the clinical use of a single large dose of ascorbic acid have resulted in the conversion of methemoglobin to hemoglobin in 56 hours.[40] Gibson[41] has shown that glutathione, normally found in red cells, exerts a strong inhibitory effect upon ascorbic acid. He has concluded that the effectiveness of this drug in the treatment of methemoglobinemia would be negligible. The use of ascorbic acid would appear to us to be limited to the treatment of the familial form of methemoglobinemia or to prevent the formation of methemoglobin by those drugs which are known to produce the pigment. In acute cases it is not recommended as an emergency measure.

## SUMMARY

1. Five cases of methemoglobinemia in infants and children are reported due to such variable causes as potassium chlorate, nitrates in well water (2), accidental ingestion of sodium nitrite tablets and sepsis.

2. A review of the literature with a report of the common etiological agents which produce this condition is included.

3. The cyanosis must be differentiated from other causes of "blue babies" with which this condition is often confused.

4. Suspected methemoglobinemia can be confirmed by (1) the characteristic chocolate color of the blood; (2) by the spectro-

scopic examination of the blood revealing the presence of an absorption band in the red region of the spectrum which can be dissipated by the addition of cyanide or alkali; (3) by spectrophotometric determination of the amount of methemoglobin present.

5. The mechanism of production of methemoglobin and the treatment of methemoglobinemia is discussed. Methylene blue should be given intravenously for rapid effect. The recommended dosage is 1.5 to 3.0 mg. per kilogram of body weight. Frequently, the higher dosage will be necessary. The drug can be used orally as an adjunct to parenteral therapy. By this route methylene blue is only one-tenth as effective.

Ascorbic acid might be of value prophylactically to prevent methemoglobin formation. It seems to be useful in the treatment of idiopathic familial methemoglobinemia. In our opinion it is not satisfactory for the treatment of cases due to poisoning.

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POLIOMYELITIS. (Revista Chilena de Pediatria, Santiago, 19: 389, May 1948). Romero and Armijo studied the clinical records of 515 children with poliomyelitis who had been observed in different children's hospitals of Santiago since 1920. The disease was previously sporadic. Since 1935 it has been epidemic. The acuteness of the disease and the number of cases increase every year. The seasonal and age distribution are similar to classical descriptions. Few cases with transitory paralysis or paresis were observed. The bulbar type was rare. In spite of the low mortality, it is believed that in future there may be more serious forms with a tendency for the disease to occur in adults.—*Journal A.M.A.*

# MULTIPLE NEURITIS AND POLIOMYELITIS

RALPH R. SCOBEY, M.D.
Syracuse, N. Y.

(*Continued from the March issue*)

## MIASMIC POISONING (*continued*)

Miasmic hematuria was observed during the Civil War and it so closely resembles the "infectious hepatitis" of World War II that it bears consideration in this report. The disease was characterized by jaundice, irritability of the stomach giving rise to uncontrollable vomiting, and a peculiar alteration in the color of the urine, generally attributed by the early writers to the presence of blood. It was regarded by some as a manifestation of malarial poisoning; by others, however, it was thought to be a modification of yellow fever. Faget (1869)[95] pointed out that this disease had frequently been seen in New Orleans but had been generally confounded by medical men with yellow fever.

Berenger-Ferand (1875)[96] showed the existence of a disease in Senegambia which corresponded with the features of the American hematuric fever. He found bile in the urine but no blood corpuscles nor hematin, except in a very small proportion of cases. Several American writers, especially one who signed his name J.H.H. (1875)[97] considered the American hematuric fever to be identical with that described by Berenger-Ferand.

Jaundice is not a common manifestation of multiple neuritis, but it can appear during the course of the disease. The most outstanding example is that resulting from phosphorus, i.e., "acute yellow atrophy". Stechele[98] observed six cases of hepatitis out of 55 cases of poliomyelitis in 1939, and in 3 out of 6 cases in 1940. Reyes[77] (1945) reported the appearance of jaundice in some of his cases of poliomyelitis. The writer[99] has also observed jaundice in a small number of cases of poliomyelitis. Van Rooyan and Kirk[100] observed a simultaneous epidemic of infectious hepatitis and poliomyelitis.

As to the manner in which miasmic poison was disseminated there was some difference of opinion. There was general agreement that it resulted from decaying vegetable matter.

Nordquist[101] states: "The essence of these various and clinically

dissimilar morbid phenomena was conceived to be an emanation from certain soils, especially those rich in vegetable matter undergoing the natural processes of decomposition under the combined influence of moisture and heat, hence swamps, marshes, river bottoms liable to floods, bayous, lagoons, ponds, dams and canals were deemed sufficient to account for the presence of the disease, especially toward the close of the summer season, when the heat was believed to operate indirectly, by lowering the water level and exposing larger surfaces of moist soil, as well as directly in promoting the generation and evolution of the malarial miasm." He considered the miasm to be the cloud that passes over marshes. "Its greater concentration or malignant character at night," he says, "was illustrated by the frequency with which men were seized on night duty. . . . It is manifest, however, that the presence of absolute swamps or marshes was not considered essential to the development of the miasm, as it was attributed to cotton lands and other soils where vegetation was rank."

The following pertinent remarks by Nordquist, which the present writer has tried to stress in his previous papers on poliomyelitis, apparently explain the reason for the spread of this disease throughout the world. "As in civil life similar consequences have often been ascribed to the clearing of timbered lands, the exposure of the soil to an increased solar heat was regarded as the cause of the newly developed insalubrity, and, as in the inception of agriculture in a new country, the removal of the undergrowth and the upturning of the soil are so frequently followed by malarial manifestations or the aggravation of pre-existing diseases, it seems likely that no inconsiderable proportion of such diseases in our armies may have been owing to the clearing of the surface and disturbance of the soil incident to the process of going into camp." It has been pointed out by others that during war and in civil life, as a result of neglect, the vegetation which becomes unusually abundant will result in a greater amount of vegetable decay during a drought.

Nordquist points out that soil-fermentation is held in check by cold and observes that excessive rains cause greater growth and the malarial manifestations lessen, but only to break out with increased virulence when this annual growth wilts and decays at the end of the rainy season.

He points out that the soldier, during the Civil War, was often hungry; his food was not infrequently poorly cooked; the issues of hard bread and fresh meat at times occasioned diarrhea; the sameness of diet developed a *scorbutic taint*. "One reporter, indeed," he says, "regarded the ration as the most powerful of the predisposing factors. . . . The soldier was often chilled at night, or after profuse perspiration or exhaustion from fatique."

Smart[83] points out that several reporters refer to impurity in the drinking water as occasioning a predisposition to malarial affections. He says that the theory of airborne swamp poison fails to account for all of the cases that occurred during the Civil War. He states: "The recognition of water as an agent in the transmission of malarial disease has been gradually effected."

White[102] pointed out that lead gave many analogous symptoms to miasmic poisoning, but he could not find lead in the water. The drinking water contained .70 of organic ammonia and he considered the samples that he examined to be swamp water. He examined and reported cistern water as veritable swamp water. Sometimes his analysis reported drinking water as resembling ditch water.

Smart[83] states regarding the drinking water: "The agency of the water-supply in the transmission of the malarial poison has an important bearing. A water free from vegetable organic matter is indicated as a means of prevention." The accepted practice of forcing fluids during illness would naturally be undesirable if the water contains a poison and no provision is made to eliminate it.

Two modern studies emphasize, as Smart points out in his observations during the Civil War, the need for greater vigilance of our water-supply. During the drought of 1930-1931, when great quantities of fish were dying in our streams, and an epidemic of gastro-intestinal disturbances was prevalent, the incidence of poliomyelitis was greatly increased; a drought was widespread throughout the country; and the streams contained great quantities of organic matter. Schaut,[103, 104] Chief Chemist of the Philadelphia Water Department, found that the water contained cyanide which resulted from the decomposition of cyanophore glucosides contained in the organic matter. He pointed out that during droughts it should be determined if cyanide is present in drinking

water and whether or not this chemical is common to all epidemics.* "More emphasis should be given the chemical and physical nature of water," he says, "rather than so much agitation about increasing the bacterial standards." He found that when chlorine was added to the water, it increased the toxicity of the cyanide.

Bertullo,[108] working in the Technological Laboratory, Fish and Wildlife Service, United States Department of Interior, College Park, Maryland, found that as the water temperature in Chesapeake Bay increases, the number of pseudomonas members increase. He has clearly shown that these forms produce sufficient hydrocyanic acid to prevent the normal fermentation of lactose by the coliform group. *"This means that you have a water supply which would be approved on the basis of the bacteriological findings and at the same time be potentially very hazardous not only from hydrocyanic acid poisoning but from intestinal pathogens."*

These facts quite evidently account for the reports during the drought of 1930-1931, when, as a result of bacteriological examinations, drinking water known to contain sewage, was declared safe to drink.

### THE THYROID GLAND IN MULTIPLE NEURITIS

The organic and chemical substances capable of producing multiple neuritis are apparently all thyroid inhibitory agents. This fact has been shown to be true with a number of the chemical substances that are listed in Table 1. The clinical features in multiple neuritis, therefore, are probably primarily the result of thyroid dysfunction with secondary effects on the other glands of internal secretion and the chemical constituents of the body. Before considering the evidence that indicates the thyroid involvement, it is important that the fundamental facts be examined.

Moehlig[109] points out that the thyroid gland has a selective action on the ectodermal tissues of the body, and through its influence on

* Recent reports by Ferrant,[105] Faucett and Miller,[106] and subsequently by others, show that nitrates in drinking water produce methemoglobinemia in babies. Liebig (1943)[107] in his book, "Chemistry and its Application to Agriculture," in discussing the decomposition of organic matter, points out that hydrocyanic acid and water contain the elements of many chemical substances, including carbonic acid, ammonia, urea, cyanuric acid, cyanilic acid, oxalic acid, formic acid, allantoin, etc. "It is well-known," he says, "that these very different substances can be obtained from hydrocyanic acid and the elements of water, by various chemical transformations." He emphasizes that there may be a disunion of the substances first formed, and in the formation the whole of the elements have assisted."

the ectodermal pituitary; also affects mesodermal tissues. The structures that belong to the ectodermal and mesodermal tissues are listed in Tables 2 and 3.

TABLE 2. *Ectodermal Tissues* (from Moehlig[109]).

a. Hair shaft (not the mesodermal hair papilla).
b. Nails.
c. Sweat, sebaceous and mammary glands (in animals: feathers, claws, horns, hoofs).
d. Epithelium of mucous membranes and their glands in vestibulum and anterior portion of the cavum oris (including salivary glands).
e. Epithelium of nares.
f. Epithelium of rectum as far as the linea sinnosa ani.
g. Dental enamel.
h. Nervous, neuroglia, and chromoffin cells of nervous system—all types of nerve cells, nerve fibers, glial cells.
i. Epithelium of smell and hearing apparatus, the organ of sight and a portion of the eye (the tapetum nigrum, the lens, the vitreous humor and muscles of the iris).
j. Epithelium of fetal coverings, the ammion and chorion.
k. The pituitary gland (both anterior and posterior lobes).

If one bears in mind the signs and symptoms which are present in all forms of multiple neuritis, regardless of the etiological poison factor, i.e., lead, arsenic, cyanide, etc., it will be observed that these

TABLE 3. *Mesodermal Tissues* (from Moehlig[109]).

2. Mesodermal tissues:
a. Connective tissues (all types of connective tissue and supporting tissues).
b. Cutis or corium, including the hair papillae.
c. Cartilage, bone.
d. Dentin and cementum of teeth.
e. Pigment cells, mesodermal.
f. Epithelium of rectum as far as the linea sinnosa ani.
g. Spleen.
h. Blood.
i. Blood vessels.
j. Fat cells.
k. Suprarenal cortex.
l. Smooth muscle (with exception of iris muscular).
m. Renal cells.
n. Nerve end corpuscles.
o. The joint cavities, the bursae, the subarachnoid and subdural spaces and their linings.
p. Pleurae, pericardium and peritoneum.
q. Sex glands and tissues.
r. Skeletal muscle, including the specialized heart muscle.

evidences are fundamentally the same as those resulting from thyroid dysfunction. Similar embryonic structures are involved in each case.

The writer[110] has pointed out that a close relationship exists between thyroid diseases and epidemic poliomyelitis. A similar relationship has been observed in other diseases characterized by multiple neuritis, notably beriberi and pellagra, particularly the latter.

In writing on pellagra, Niles[111] points out that in Lombardy, where there is much goiter and cretinism, physicians regard one disease as the cause of the other. Morse[112] indicates that the signs and symptoms of pellagra suggest disease of the thyroid, adrenal and parathyroid. He found changes in the thyroid gland more striking than in any other organ. "The picture suggests", he states, "not so much an infective process as the reaction of some chronic intoxication with gradual destruction of the gland by the inflammatory reaction. There is the diffuse sclerosis due to some diffused chemical irritant." Hellwig and Sussman[113] frequently observed atrophy of the thyroid gland in pellagra. Ornstein[114] reported from a study of 25 women and 10 men in different stages of pellagra, that the blood cholesterol was high in most of their cases.

Shelley[68] points out the parallel signs and symptoms of myxedema and pellagra. He states that the thickened, rough skin; slight edema; dry scaly skin; swollen tongue; and mental dullness and apathy of each of these diseases is very striking. He says: "From these observations it seems that the toxin of pellagra produces changes in the thyroid gland leading to an insufficiency of thyroxin being excreted with results that pellagra in some respects resembles myxedema." Shelley, as well as others, have been successful in the treatment of pellagra with thyroid extract.

Grey,[115] in studies on beriberi in Japan, describes a pre-beriberi state which appears to condition the individual to beriberi. The present writer[116] described a similar condition which was observed in his patients during the past war and appeared to be related to protein deficiency. A striking fact that was observed at that time was that the manifestations of vitamin deficiencies that were present did not respond to vitamin preparations as expected until the protein deficiency was corrected. The writer[117] has also observed

these same signs and symptoms in a great percentage of school children. He concluded that a state of hypometabolism probably existed, involving primarily the thyroid gland.

Grey[115] observed in this pre-beriberi condition that healthy appearing individuals* were exhausted without apparent cause; incapable of physical effort; and complained of palpitation of the heart and faintness and difficulty in breathing. The bodies of these individuals were not at all emaciated; the skin in many cases was rough and the coarseness or brawny condition of the extremities was obvious. In many cases there was loss of appetite, and often constipation; in practically all cases there was anemia.

Grey points out: "In order to obtain sufficient nourishment the Japanese people are obliged to consume larger quantities of food." He stresses the inadequate amounts of proteins that are found in the diets of rice-eating countries. He states: "*Clearly, therefore, for the vitamin catalyst to work there must be material for it to work upon, in other words a diet balanced within reasonable limits. . . . Polyneuritis has been warded off by administration of nitrogenous preparations. There is the possibility also that there is a deficiency not merely of total nitrogen but that certain special nitrogenous substances are needed to cooperate with the vitamins.*" He further adds: "The fact that the body temperature of rice-eating people, such as the Japanese and Chinese, is about a degree lower than that of most races, is surely suggestive, as is also the fact observed by certain Japanese workers, such as Koroidzume[116] and Earle[117] in Hong Kong, that the basal metabolism of Japanese and Chinese people is definitely lower than that of Europeans living in the East."

Grey's reference to sudden outbreaks of beriberi is significant and corresponds with the present writer's ideas in regard to poliomyelitis. "They may be explained in this way," he says, "namely the stimulation of a tissue which is not in a fit state to be stimulated." The fact that the thyroid gland is suddenly overstimulated in beriberi is suggested by the successful use of iodine in the treatment of this disease. The beneficial effects of nicotinic acid in cases of pellagra, on the other hand, might be attributed to the stimulation of a thyroid gland that is underfunctioning. The signs and symptoms of nicotinic acid intoxication resemble those of hyperthyroidism, i.e., tremor, flushing, sweating, tachycardia,

*See footnote, p. 112 (March 1949).

etc. Several workers have employed pituitary extract in the treatment of pellagra; others have employed thyroid extract. It would appear that the former stimulates the thyroid gland in this disease through the thyrotrophic hormone of the pituitary and the latter stimulates it directly.

It seems evident that vitamin deficiencies arise when the thyroid is inhibited by poisonous substances, rather than because vitamins are lacking in the diet. Vitamin deficiencies follow because of the fact that there is a disturbance of cellular metabolism and dysfunction of the liver. The frequent observation that beriberi and pellagra develop in individuals receiving good diets and that there is unresponsiveness of these diseases in many patients to a balanced diet or vitamin supplements would indicate the fact that the thyroid inhibitory substance is still operative or has produced an undesirable effect.

Eppinger and Arnstein[118] remarked that polyneuritis probably occurs more often in connection with disease of the liver than one would expect from the literature. They concluded that a toxin retained in the liver or one unchanged in the intestine might be responsible for the development of neuritis, or that hepatic insufficiency and polyneuritis might both be the result of a third factor. They suggested that this third factor might be a fluorescent substance, such as hematoporphyrin.

It appears to be of great significance that the extrinsic poisons mentioned in this report which are capable of producing multiple neuritis likewise produce porphyria. The present writer[119] has pointed out the intimate relationship of the porphyrias and poliomyelitis. In both of these conditions, as well as in beriberi, pellagra, toxemia of pregnancy and rheumatic fever, increased amounts of porphyrins are found in the urine. Evidence of hepatic insufficiency is evident in all of these conditions and has been demonstrated at autopsy. The first reference that the writer has been able to find regarding an increased excretion of porphyrins in the urine is the mention of a "dark or very red urine" in connection with "miasmic poisoning."[88]

Wayburn and Guerard[119] state regarding the liver in multiple neuritis: "These are associated in too high a percentage to be coincidental, two diseases, one with and one without etiological

factors. If peripheral neuropathy may be regarded as a fairly reliable sign of deficiency of vitamin $B_1$, the obvious inference is that there is in cases of cirrhosis a deficiency of thiamin. It does not follow that thiamin deficiency is the cause of hepatitis or that thiamin protects the liver." Frazier and Rovdin,[120] as well as Means[121] have pointed out that in patients with exophthalmic goiter there are often symptoms suggesting thiamin deficiency.

Wechsler[8] states that the avitaminosis in multiple neuritis is due not so much to lack of food, although that too is a factor, as to the inability to digest, assimilate or metabolize because of disease which originally had nothing to do with avitaminosis. He states: "It is well-known of course that avitaminosis causes loss of appetite, which in turn prevents ingestion of vitamins, thus establishing a vicious circle. . . . *One is not only dealing with a specific poison but with an additional avitaminosis.*"

The work of Sure and Dichek[122] suggests that vitamin $B_1$ may have an antigoitrogenic effect. They found that it has a sparing action on body catabolism. This effect might be the result, in part at least, to the sulphur in the thiamin molecule, as suggested by the present writer,[123] which would act as a detoxicant of poisons. The experiments of Badger and Masunaga[124] indicate that calcium deficiency interferes with the utilization of vitamin $B_1$. In thyrotoxicosis there is an excessive loss of calcium. Sure and Theis[125] found a reduction of vitamin C in the tissues in vitamin A and $B_1$ deficiencies produced by thyrotoxicosis, thus establishing a vitamin interrelationship. Peters and Rossiter[126] noted a fall in tissue cocarboxylase in hyperthyroidism.

Williams et al.[127] have noted an interrelationship of the vitamins in hyperthyroidism, pellagra and ariboflavinosis. The presence of vitamin deficiencies in thyroid dysfunction, other than the B-complex, has frequently been observed by other writers.

One outstanding fact that appears to have been noted by the physicians during the Civil War is that the soldiers who were most susceptible to the "miasmic poison" had a *scorbutic taint*. This fact has been noted in regard to pellagra and other forms of multiple neuritis. Spies et al.[128] noted that the diets of patients with pellagra were low in ascorbic acid. Goldsmith et al.[129] made similar observations and concluded that pellagra is often accompanied by a vitamin C deficiency. Minnish et al.[130] found vitamin C deficiency

in cases of pellagra, beriberi and riboflavin deficiency. Beyer[131] and others have found that vitamin C protects the liver against liver damage produced by chemical poisons. Vedder[132] considered that there is a resemblance of pellagra, scurvy and beriberi and compared the changes in the nervous system with those of beriberi. The present writer[110] pointed out in a previous report the important role of vitamin C as a detoxicant; its antigoitrogenic action; its relationship to the nervous system; and among other physiological properties, its hepatic protective action. It was also pointed out that there is an intimate relationship between vitamin C and calcium in intercellular metabolism.

Deficiencies not only of the vitamins occur in thyrotoxicosis but there is also a loss of nitrogen and calcium. Durham[133] observed from the beginning of beriberi, a negative nitrogen, phosphorus and calcium balance. This observation was also reported by Schauman[134]. That there is a loss of zinc from the body in beriberi is indicated by the fact that Eggleton[135] found the zinc content of the epidermal structures in this disease greatly reduced. This finding induced him to suggest that zinc deficiency may be a factor in the beriberi syndrome. Zinc deficiency in animals has been found by Follis, Day and McCollum[136] to produce skin lesions, which as described by them, resemble those observed in pellagra. Excretion of zinc in excessive amounts has been reported in the porphyrias.

The accumulation of pyruvic acid in the blood in thiamin deficiency states is noteworthy. The oxalates are formed from pyruvic and acetaldehyde—intermediate products of the oxidation of the sugars—which with incomplete oxidation form dibasic acids. Thus, in diseases of the nervous system, liver disturbances, arthritis, diabetes mellitus, and under the influence of adrenalin, thyroxine, and anoxemia, the endogenous oxalates are increased. Urinary oxalate is elevated on exposure to hydrocyanic acid. Jurgens and Spehr[137] found that the blood sugar and oxalic levels tended to parallel each other.

Further evidence could be presented to show that an exogenous toxic substance, capable of producing multiple neuritis, results primarily in an inhibition of the thyroid gland, followed by a disturbance of the other glands of internal secretion; liver dysfunction; a disturbance of tissue metabolism; disturbances in protein, fat and carbohydrate metabolism, vitamin and mineral deficiencies;

and with resultant undesirable effects on the ectodermal and mesodermal structures of the body.

### HEART AND OTHER STRUCTURES IN MULTIPLE NEURITIS

It has frequently been observed that the heart is involved in cases of multiple neuritis. "It is also essential," Walshe[10] states, "to bear in mind that an active peripheral neuritis is always associated with some affection of the heart muscle, that this is an integral part of the illness and sometimes even the cause of death in cases that end fatally. . . . The diversity of etiological factors, contrasted with the uniformity of the illness raises the question whether these factors act directly upon peripheral nerves and myocardium to produce the same result, or whether they may not all act indirectly and in virtue of some common disorder of metabolism caused by them, in the course of which a common toxic metabolite is produced, to become in turn the direct poison of the nervous system and heart muscle. The case of tropical nutrition disease, beriberi, gives a clue to this problem."

Similar observations have been made in regard to the heart in epidemic poliomyelitis. Landon and Smith[44] found cardiac dilatation at autopsy in 73 out of 83 cases of poliomyelitis studied. Another feature in their cases was the tendency to myocardial degeneration.

It has already been pointed out that in "miasmic poisoning" the clinical picture often resembled and was confused with rheumatism. Smart[83] states: "Rheumatism and neuralgia are also suggested as consequent upon the malarial influence". In other forms of multiple neuritis, arthritis is not infrequently present. Cobb and Coggeshall,[6] in referring to the relationship of polyarthritis and polyneuritis, state: "It is important to mention the analogy to the clinical syndrome called 'polyarthritis'; there probably is a significant relationship. A great many cases of polyneuritis associated with arthritis are never seen by the neurologist because the internist treats the main symptoms and knows that, if he cares for the joint, the nerves will probably follow suit. Involvement of the muscles frequently occurs with arthritis, but myositis is rarely diagnosed, although lame, stiff, tender muscles are one of the chief symptoms, all too frequently neuritis is overlooked, even when marked muscular atrophy is present. In fact, it should be

emphasized that the old fashioned term 'rheumatism' (including as it should myositis, arthritis and neuritis) is a much better term than 'arthritis' just because it is inclusive; moreover, 'rheumatism' is a disease treated by general practitioners, and 'arthritis' tends to drift to orthopedic specialists."

The kidneys, in cases of multiple neuritis, regardless of the poisonous etiological factor, usually show changes similar to those observed in *lipoid nephrosis*. In the examination of the kidneys in the cases of poliomyelitis described by Landon and Smith,[44] there was a varying degree of granular and even fatty degeneration of the tubular epithelium. Grossly the kidneys not infrequently suggested lipoid degeneration of the parenchyma. There was frequently encountered a rather striking albuminuria evidenced by a pink staining granular precipitate in the capsular spaces and tubules.

A finding of great significance in Landon and Smith's pathological examinations in cases of poliomyelitis was the condition of the thymus gland. This structure is almost regularly appreciably enlarged, intensely congested, and often moderately edematous. "In the older age group, twenty-five years and over, the invariable persistence of the thymus as an active hyperplastic organ was particularly noteworthy."

These findings correspond with those observed in cases of thyrotoxicosis. Marine[138] states that the thymus gland is enlarged in 70 to 90 per cent of the primary cases irrespective of age.

The other lymphoid structures in poliomyelitis are regularly involved to such an extent that Burrows[139] suggested that poliomyelitis is an "acute lymphatic hyperplasia." In the case of thyrotoxicosis, Marine[138] says: "The literature emphasizes enlargement of the cervical lymph nodes, whereas actually all the lympoblastic tissues are enlarged, and in the typical cases a picture identical with that seen in status lymphaticus is present. . . . During the developmental stage of goiter there is frequently a relative lymphocytosis. This may be associated with enlarged tonsils, adenoid growths, enlarged spleen and other evidence of status lymphaticus which is relatively common in association with endemic goiter."

The blood picture reflects this pathological picture often by showing a characteristic relative increase in lymphocytes and mononuclears in cases of multiple neuritis. Blood counts of this

character are likewise found in states of thyroid dysfunction.

Naegeli (1931)[140] felt that the adrenals seemed to be most definitely involved in the control of the lymphoid tissues. In Addison's disease, which has frequently been reported in association with beriberi and pellagra, there is usually a marked lymphocytosis resembling status lymphaticus at autopsy. "It suggests that the adrenals have an inhibitory effect on lymphoid tissues, a view which is confirmed by experiments such as those of Zwemer and Lyons who found in adrenalectomized animals an increase in the blood lymphocytes. It is probably the cortex of the adrenal which has this inhibitory function. As far as the medulla of the adrenal is concerned, it has long been known that adrenalin may produce marked lymphocytosis."[141] Landon and Smith[44] frequently found, in cases of poliomyelitis at autopsy, extreme congestion of the adrenals with medullary hemorrhage.

Achlorhydria or hypochlorhydria is an almost constant accompaniment of multiple neuritis. Wechsler[8] states concerning it. " . . . It is of more than passing interest that in practically all cases, no matter from what cause in which the gastric contents were examined, free hydrochloric acid was either entirely absent or reduced almost to zero." Achlorhydria is common in cirrhosis of the liver and it is likewise associated with the various nutritional deficiency states. In cases of thyroid dysfunction, there is likewise achlorhydria.

## CONCLUSION

Among the many possible conclusions suggested by this report, there seems to be indicated the obvious necessity to follow the correlation of multiple neuritis and related diseases, and also to carry poliomyelitis research as to causes beyond the present limitation of the so-called virus theory into the basic topographical chemical reactions which cause breakdown in the functioning of the human organism.

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1411 *South Salina Street.*

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RELATION BETWEEN CHICKENPOX AND HERPES ZOSTER. (Dermatologica, Basel, 96: 373, No. 5, 1948). Fellner reports histories of 3 children who contracted chickenpox. First chickenpox developed in a boy, age 7. Seventeen days later chickenpox appeared in a cousin, a little girl of 2 years, and eleven days later an older sister of this little girl showed the exanthem of chickenpox. Herpes zoster appeared in the mother of these 2 girls five days after the chickenpox had developed in the older girl. Whereas in the first 2 children the chickenpox took a mild course, the third child had an extremely severe eruption and serious general manifestations, probably due to the simultaneous occurrence of herpes tonsurans vesiculosus, which probably induced hyperallergy in the skin.—*Journal A.M.A.*

PSYCHIC DISTURBANCES ASSOCIATED WITH TUBERCULOUS MENINGITIS. (Semaine des Hôpitaux de Paris, 24: 2004, Aug. 18, 1948). Scherrer reports the occurrence of psychic disturbances in 21 of 30 patients with tuberculous meningitis in the first phase of the disease. The great majority of the patients were children and adolescents. Streptomycin therapy was instituted within one to ten days after the appearance of clinical signs of meningitis. The psychic disturbances consisted essentially of reduced consciousness reaching from a diminution of attention to stupor and to an anxiety state. The patients presented temporospatial disorientation, enuresis and occasionally hallucinations. The psychic disturbances were precocious and showed a tendency to regression on treatment with streptomycin. Dynamics of the cerebrospinal fluid may play a part in the pathogenesis of the mental confusion and amnesia seen in tuberculous meningitis.—*Journal A.M.A.*

# CLINICAL REVIEWS

*In order to encourage the writing of clinical articles by recent graduates or senior medical students, the* ARCHIVES *will publish monthly at least one such paper from the classes of Doctor Reuel A. Benson, New York Medical College, New York; Doctor Philip Morn Stimson, Cornell Medical School, New York, and Doctor John A. Toomey, Western Reserve University Medical School, Cleveland. Other interested medical schools are cordially invited to submit student papers for consideration.*

## TWO FACTORS IN THE DIFFERENTIATION OF RHEUMATIC AND NON-RHEUMATIC TYPES OF SYDENHAM'S CHOREA*

### A STUDY OF 97 CASES

ROBERT L. SHERMAN, M.D.
AND
I. HOWARD KAISER, M.D.
New York.

In a recent article, Kagan and Mirman[1] presented a survey of 107 cases of Sydenham's chorea. The disease was considered in terms of the relationship of erythrocyte sedimentation rate and psychogenic factors to the diagnosis and differentiation of rheumatic and non-rheumatic chorea.

The present paper is a comparative study based on 97 cases of Sydenham's chorea admitted to the Metropolitan Hospital during the eleven-year-period from 1936 through 1947. We concerned ourselves primarily with the relationship of the erythrocyte sedimentation rate to cases of chorea with established rheumatic complications and to those uncomplicated or so-called non-rheumatic cases, and with a comparison of the incidence of psychic disturbances in rheumatic and non-rheumatic chorea.

A number of arbitrary liberties were taken in evaluating the material for the purpose of simplification of study. We considered only those cases with adequate histories and upon whom erythrocyte sedimentation rates were done. The sedimentation rate technique used in this study was the Westergren method with an allowable normal range of 10 to 18 mm. per hour. Active rheu-

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matic fever was diagnosed without the aid of the sedimentation rate, since this very factor was primarily under consideration. Polyarthritis, diastolic murmurs, positive x-ray or EKG findings, and fever were the criteria used in making a diagnosis of an active rheumatic process. Of these, fever associated with either polyarthritis or diastolic murmur was considered sufficient in itself, the other factors being used as corroborative evidence.

Where the history of past rheumatic fever was in question, x-ray findings of a mitralized heart or EKG tracings showing persistently prolonged P-R intervals were considered adequate for the diagnosis. Many apical systolic murmurs were encountered. In most cases, they were equivocal, and in all cases they were disregarded as a diagnostic criterion for rheumatic fever when they appeared alone. This step was taken despite the association by some authors of apical systolic murmurs with rheumatic fever and chorea, for it was felt that in the absence of other rheumatic signs a positive organic etiology of these murmurs was lacking.

It will be noted in the ensuing charts and discussions that the nature of psychogenic factors has not been delineated. It would be well to clarify this point at present. In our original study, said factors were divided into two major categories. The first and smallest one, seven cases, included those situations in which the choreic attacks were precipitated spontaneously by known psychic trauma. Of these seven cases, five attacks commenced following a severe fright, including man entering through a fire escape; near escape from an auto accident; dog jumping on face; a thunder storm; and being lost. Of the remaining two, one attack followed a demotion in school, and the other was admittedly utilized as a method for avoiding school. The second category, twenty-three cases, was made up of cases in which psychogenic backgrounds were noted. This general group included mentally retarded patients, those with enuresis from birth to seven years of age or more, cases of marked domestic incompatibilities, and general behavior problems.

## DATA

For purposes of simplification and clarification we have divided the series into three major categories:

I. Those seen during the first choreic attack, with no follow-up.

II. Those seen during the first attack and subsequent recurrences.

III. Those first seen during a choreic recurrence, some of whom were subsequently followed.

These categories have been considered from two viewpoints: the relationship of the erythrocyte sedimentation rate to chorea associated with rheumatic fever, active or historical; and the incidence of psychogenic disturbances in rheumatic and non-rheumatic chorea.

GROUP I

Group I consists of fifty-eight cases, representing 59.8 per cent of the total series. These cases were followed in the hospital for an average duration of 6.2 weeks, ranging from 1 to 20 weeks. Pertinent data is tabulated in Chart 1a and b. It may be seen

CHART 1a. *First Choreic Episode (E.S.R.)*

| | No. | Hist. of or active R.F. | % |
|---|---|---|---|
| Elevated E.S.R. | 32 | 23* | 71.9 |
| Normal E.S.R. | 26 | 6 | 23.2 |
| Totals | 58 | 29 | 50.0 |

*Three of these had questionable histories and one had questionable polyarthritis.

CHART 1b. *First Choreic Episodes (Psych.)*

| | No. | Psych. | % |
|---|---|---|---|
| History of or active rheumatic fever... | 29 | 4 | 13.8 |
| Non-rheumatic | 29 | 11 | 37.9 |
| Totals | 58 | 15 | 25.9 |

that of the fifty-eight patients observed during their first choreic episodes, thirty-two had increased erythrocyte sedimentation rates, or 55.2 per cent of Group I. Of these thirty-two, nineteen either gave a history of or evidenced definite signs of rheumatic fever. An additional three cases gave questionable rheumatic fever histories, and one more had questionable polyarthritis. These latter cases were included with the nineteen, giving a total of twenty-three with rheumatic manifestations, or 71.9 per cent of the cases in this category with elevated erythrocyte sedimentation rates. None of the remaining nine cases with increased sedimentation rates showed rheumatic signs.

Concerning the twenty-six cases with normal erythrocyte sedimentation rates, it should be mentioned that five showed rheumatic activity at the time seen, and one additional case gave a history of rheumatic fever, an incidence of 23.2 per cent with rheumatic complications.

Psychogenic factors were considered in terms of their relationship to rheumatic and non-rheumatic chorea. Of the twenty-nine cases of rheumatic chorea, four (13.8 per cent) had psychiatric disturbances. Three of these were general factors, one was specific. By comparison, eleven (37.9 per cent) of the twenty-nine cases of non-rheumatic chorea presented psychogenic complications, five of which were specific.

GROUP II

Group II, those cases seen during their first choreic attacks, with follow-up studies, consists of twenty cases, or 20.6 per cent of the total series. These patients were followed for an average of 2.1 years and represent a total of fifty-six attacks. Nine of these (45 per cent of this group) had an increased erythrocyte sedimentation rate on either the first or subsequent attacks. Four, 44.4 per cent of the nine, had either a history of or active rheumatic fever. Of the remaining eleven (55 per cent of the total twenty cases), or those with normal sedimentation rates, five (45.5 per cent) had a history of or active rheumatic fever. The above is tabulated in Chart 2a and b.

It will be noted from Chart 2b that the erythrocyte sedimentation rate in nine cases underwent a change from one attack to the next. Five cases, Nos. 32, 97, 6, 31 and 42, showed normal sedimentation rates on their initial attacks of chorea and subsequently changed to increased sedimentation rates. Cases 6 and 42, followed for two and four years, respectively, at no time showed signs of or gave a history of rheumatic fever. Both of these were observed during three choreic episodes. Case 6 went from a normal to an increased sedimentation rate on the second attack and returned to normal on the third attack. Case 42 had a normal sedimentation rate on the first two attacks, and an increased one during the third episode. The remaining three cases, 32, 31 and 97, had associated rheumatic complications. Case 32 was seen during two attacks. The first was associated with active rheumatic fever and a normal sedimen-

tation rate. On the second attack the sedimentation rate was increased. Case 31 was seen during three attacks. The first attack, free of rheumatic complications, showed a normal sedimentation rate. The second, still free of rheumatic complications, was marked by a change to an increased sedimentation rate, while in the final attack active rheumatic fever was manifested, along with an increased sedimentation rate. Case 97, seen twice, presented a history of rheumatic fever, and the sedimentation rate changed from normal on the first episode to an increased one on the follow-up.

CHART 2a'. *First Choreic Attacks With Follow-Ups (E.S.R.)*

| | No. | Hist. of or active R.F. | % |
|---|---|---|---|
| Elevated E.S.R.* | 9 | 4 | 44.4 |
| Normal E.S.R. | 11 | 5 | 45.5 |
| Totals | 20 | 9 | 45.0 |

*On first or subsequent attacks.

CHART 2a". *First Choreic Attacks With Follow-Ups (Psych.)*

| | No. | Psych.* | % |
|---|---|---|---|
| History of or active rheumatic fever | 9 | 2 | 22.2 |
| Non-rheumatic | 11 | 5 | 45.5 |
| Totals | 20 | 7 | 35.0 |

*All non-specific.

Four (Cases 84, 66, 48 and 78) of the nine cases which showed changes in the sedimentation rates exhibited increased sedimentation rates on their initial attacks and subsequently became normal. Cases 48 and 78 were seen twice each. Neither was associated with rheumatic complications, and in both cases the elevated sedimentation rate seen during the first attack became normal on the follow-up. Active rheumatic fever and an elevated sedimentation rate were both present during the first choreic episode in Case 84. A normal sedimentation rate was observed during the second attack, this changing to an increased one on the third attack. Case 66 presented itself with a history of rheumatic fever, and the increased sedimentation rate reported during the first choreic attack became normal on recurrence.

Psychogenic disturbances were noted in seven of the twenty patients comprising Group II. Two of these were observed among the nine cases associated with rheumatic complications, an inci-

CHART 2b. *An Analysis of Group II*

| Case No. | Time Followed | History of R.F. | Active R.F. | E.S.R. 1st Attack | Subsequent E.S.R. | Psych. Factor |
|---|---|---|---|---|---|---|
| 84 | 2 yrs. | — | + | Elevated | Norm. on 1st recur.; elev. on 2nd recur. | 0 |
| 86 | 3 yrs. | + | + | Elevated | Same on four recurrences | 0 |
| 19 | 4 mos. | + | + | Normal | Same on one recurrence | 0 |
| 32 | 1 yr. | — | + | Normal | Elevated on 1st recur. | Background |
| 58 | 1 yr. | ? | + | Normal | Same on 1st recurrence | Background |
| 66 | 3 yrs. | + | — | Elevated | Norm. on 1st recurrence | 0 |
| 61 | 4 mos. | + | — | Normal | Same on 1st recurrence | 0 |
| 97 | 1 yr. | + | — | Normal | Elevated on 1st recur. | 0 |
| 31 | 2 yrs. | — | ∓* | Normal | Elevated on 2nd recur. | 0 |
| 48 | 1 yr. | — | — | Elevated | Norm. on 1st recurrence | 0 |
| 63 | 2 mos. | — | — | Elevated | Same on 1st recurrence | Background |
| 78 | 3 yrs. | — | — | Elevated | Norm. on 1st recur. | 0 |
| 6 | 2 yrs. | — | — | Normal | Elev. on 2nd; norm. on 3rd recurrence | Background |
| 4 | 6 yrs. | — | — | Normal | Same on four recurrences | 0 |
| 12 | 4 mos. | — | — | Normal | Same on two recurrences | Background |
| 20 | 3 yrs. | — | — | Normal | Same on two recurrences | 0 |
| 33 | 2 yrs. | — | — | Normal | Same on one recurrence | 0 |
| 37 | 6 yrs. | — | — | Normal | Same on four recurrences | Background |
| 42 | 4 yrs. | — | — | Normal | Same on 1st; elev. on 2nd | 0 |
| 71 | 1 yr. | — | — | Normal | Same on 1st recurrence | Background |
| Totals: 20 cases | 2.1 yrs. Average | 5 + 1? | 6 | 6 elev. 14 norm. | 5 elev.—N 6 N—elev. | 7 Backgrounds |

*Negative first attack; positive third attack.

dence of 22.2 per cent. Five of the eleven non-rheumatic cases gave evidence of a psychogenic factor, an incidence of 45.5 per cent (see Charts 2a′ and a″).

GROUP III

Those cases first seen during a recurrent episode of chorea, some of which were followed, comprise Group III. There are nineteen cases in this category, representing 19.6 per cent of the total series. Twenty-four attacks were observed in this group. Of the six cases (31.6 per cent of Group III) with elevated sedimentation rates, four had rheumatic complications, a rate of 66.6 per cent. By comparison, four patients of the remaining thirteen (68.4 per cent of Group III) with normal sedimentation rates gave a history of or showed signs of active rheumatic fever, a rate of 30.8 per cent.

Included in the six cases with elevated sedimentation rates is one, Case 22, seen twice, on the first and second recurrences, who gave a history of rheumatic fever and showed active signs of same. When first seen, a normal sedimentation rate was observed. This became elevated on the second recurrence.

CHART 3a. *First Seen With Recurrences (E.S.R.)*

| | No. | Hist. of or active R.F. | % |
|---|---|---|---|
| Elevated E.S.R.* | 6 | 4 | 66.6 |
| Normal E.S.R. | 13 | 4 | 30.8 |
| Totals | 19 | 8 | 42.1 |

*First or subsequent recurrences.

CHART 3b. *First Seen With Recurrences (Physc.)*

| | No. | Psych. | % |
|---|---|---|---|
| History of or active rheumatic fever | 8 | 1 | 12.5 |
| Non-rheumatic | 11 | 7* | 63.6 |
| Totals | 19 | 8 | 42.1 |

*One specific.

Psychogenic complications were noted in eight of the nineteen cases, or 42.1 per cent of the group. One of these appeared in the group of eight with rheumatic manifestations, a rate of 12.5 per cent. Seven were noted in cases of non-rheumatic chorea, a rate of 63.6 per cent. Only one of the eight cases with psychogenic disturbances revealed a specific psychogenic relationship with the attack. It appeared in a case of uncomplicated chorea. These data are summarized in Charts 3a and b.

SUMMARY OF DATA

A summary of the preceding groups studied will reveal the following interesting figures: Of the total ninety-seven cases studied, forty-seven (48.5 per cent) were encountered with an elevated sedimentation rate. Thirty-one of these, or 65.9 per cent of those with elevated sedimentation rates, had rheumatic complications. On the other hand, only fifteen of the remaining fifty cases (51.5 per cent of the total), all of which had normal sedimentation rates, gave a history of or showed signs of active rheumatic fever, a 30 per cent incidence.

In considering the psychogenic aspects of the series, thirty cases, or 30.9 per cent of the total ninety-seven, were observed. Seven of these (six with general causes and one specific) were observed in the group of forty-six cases (47.3 per cent of the total) of rheumatic chorea, an incidence of 15.2 per cent. Of the fifty-one cases (42.7 per cent of the total), twenty-three were found to be associated with psychogenic factors (seventeen with general causes and six specific), an incidence of 45.1 per cent.

These totals represent a simple tabulation of all the data presented heretofore, and the same generalities and liberties as set out in the introduction were employed in this final computation (see Charts 4a and b).

CHART 4a. *Grand Totals (E.S.R.)*

| | No. | Hist. of or active R.F. | % |
|---|---|---|---|
| Elevated E.S.R. | 47 | 31* | 65.9 |
| Normal E.S.R. | 50 | 15 | 30.0 |
| Totals | 97 | 46 | 47.4 |

*Four have either questionable histories or present signs of rheumatic fever.

CHART 4b. *Grand Totals (Psych.)*

| | No. | Psych. | % |
|---|---|---|---|
| History of or active rheumatic fever | 46 | 7* | 15.2 |
| Non-rheumatic | 51 | 23† | 45.1 |
| Totals | 97 | 30 | 30.9 |

*One specific. †Six specific.

DISCUSSION

It would seem reasonable to conclude from the above data that the sedimentation rate is more often elevated in cases of rheumatic than in non-rheumatic chorea. In our series the comparative percentages were 65.9 per cent in the first and 34.1 per cent in the latter. While this generalization seems justifiable, we would limit the value of the erythrocyte sedimentation rate as a diagnostic criterion in the differentiation of these two classes, since a total of thirty-one cases fails to fall within this generalization. It can be seen from Chart 4 that sixteen cases were observed in which the sedimentation rate was increased without any associated rheumatic complications. We have reported an additional fifteen cases with rheumatic manifestations, yet the sedimentation rate remained normal. We feel that this total of thirty-one cases, or 32 per cent of the series not falling within the generalization, is too high a deviation to permit the use of the sedimentation rate as an important factor in the differential diagnosis of choreas.

We also discussed previously ten cases individually in which the sedimentation rate changed on subsequent attacks. Nine of these ten were observed during their first choreic episodes (see Chart 2). This figure represents almost half of the twenty-four cases seen more than once. Of six cases which had initially normal sedimentation rates subsequently becoming increased, four had rheumatic complications. Four cases exhibited increased sedimentation rates on the initial attack and subsequently became normal. Two of these were at all times non-rheumatic. We see, therefore, that the latter four cases, and the two remaining of the first six do not follow Kagan and Mirman's maxim that recurrences of initially rheumatic chorea remain rheumatic, and that non-rheumatic recurrences remain as such. In all fairness, however, it must be admitted that only 25 per cent of the twenty-four cases we followed failed to meet their standards, a number too small to be awarded great significance.

It is interesting to note that in a review of 140 cases of chorea, Schwartzman et al.[2] reported rheumatic complications in 50.5 per cent of their series. At the same time, however, they recorded only a 27.9 per cent incidence of elevated erythrocyte sedimentation rates. Although no attempt is made to divide these elevated sedimentation rates into rheumatic and non-rheumatic groups, it may

be noted that even if we assume that they all fall into the rheumatic group, this still leaves almost 50 per cent of rheumatic choreas with normal erythrocyte sedimentation rates.

From our data it is apparent that psychic disturbances are more commonly associated with non-rheumatic than with rheumatic chorea, 45.1 per cent as compared to 15.2 per cent. While it is true that only seven of these psychogenic disturbances are specifically related to choreic episodes (six appearing in the non-rheumatic group, the other in a rheumatic patient), the remaining twenty-three cases show a distribution of seventeen in the non-rheumatic group and only six in the rheumatic, a difference worthy of consideration. One is still not wholly justified in assigning to psychogenic disturbances a major etiological role in the causation of Sydenham's chorea, but we feel that this factor is worthy of further consideration and study, especially in non-rheumatic chorea.

## SUMMARY

1. Ninety-seven cases of Sydenham's chorea were reviewed.

2. 47.3 per cent of the series was associated with rheumatic complications.

3. The sedimentation rate was elevated in 48.5 per cent of the series.

4. 65.9 per cent of those cases with elevated sedimentation rates had rheumatic complications.

5. 30 per cent of those cases with normal sedimentation rates had rheumatic complications.

6. Psychogenic disturbances were noted in 30.9 per cent of the series.

7. 15.2 per cent of the rheumatic choreas had psychic complications.

8. 45.1 per cent of the non-rheumatic choreas had psychic complications.

## CONCLUSIONS

1. Chorea may be either rheumatic or non-rheumatic.

2. Elevated erythrocyte sedimentation rates are more frequently encountered in rheumatic than in non-rheumatic chorea.

3. Psychogenic complications are more frequently encountered in non-rheumatic than in rheumatic chorea.

4. Psychogenic complications occur frequently enough to be considered as one of the etiological factors in the production of Sydenham's chorea.

5. Erythrocyte sedimentation rate determinations as well as psychogenic factors may be of aid in the differentiation of rheumatic and non-rheumatic chorea, but their value is limited.

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VIRUS DISEASES AND THEIR EFFECT ON FETUS. (Nordisk Medicin, Stockholm, *37*: 409, Feb. *27*, 1948). Grönvall and Salender's investigations show that maternal German measles, mumps, acute hepatitis and acute anterior poliomyelitis can be fraught with danger for the fetus. German measles in pregnancy has been less dangerous for the fetus in Sweden than in Australia.—*Journal A.M.A.*

STREPTOMYCIN IN ABDOMINAL TUBERCULOSIS. (Revista Chilena de Pediatrica, Santiago, 19: 371, May 1948). Matte and his collaborators gave streptomycin to 10 children, between the ages of 6 and 12 years, with intestinal, peritoneal or both forms of tuberculosis. The disease was acute in all cases. It complicated pulmonary tuberculosis in some of the cases. The drug was administered in daily doses of 1 Gm. for the first and 0.5 Gm. for the second month. In some cases the treatment lasted for three consecutive months on the same dose schedule. The daily dose was given in fractional doses at intervals of eight hours for the first month and of six hours for the second month. Immediate and late results were satisfactory. The good results persist, after a period of two to seven months after discontinuation of the treatment.—*Journal A.M.A.*

# CLINICAL-PATHOLOGICAL CONFERENCE

WILLARD PARKER HOSPITAL, NEW YORK

*Meeting held February* 15, 1949

DR. PHILIP MOEN STIMSON, presiding.

## ERYTHEMA MULTIFORME BULLOSUM

DR. SILVERBERG presented Case No. 4990, a fourteen-year-old white female, who was admitted to Willard Parker Hospital from another hospital on October 7, 1948, as a possible case of skin diphtheria.

*History of Present Illness.* Illness dates back to March 15, 1948 when she developed sores and blisters in the mouth. These were treated by her private physician with gentian violet and penicillin lozenges. Slight improvement was noted, but the lesions recurred three days later. The patient was taken to a hospital where she received acriflavine mouth washes and intramuscular penicillin During her hospitalization there she developed a purulent discharge from both eyes, blisters on the hands and complained o. burning on urination. She remained at the hospital for six weeks and was sent home improved. Twenty-four hours after her arrival home, she developed generalized red patches, and was taken to another hospital. On admission there on May 12, 1948, the patient was observed to have urticarial and erythema multiforme-like eruptions, with conjunctival, oral and vulva involvement. Her course at the hospital was febrile with occasional flare-ups of the erythema multiforme lesions. The lesions on the trunk cleared spontaneously, but she continued to have lesions on the genitalia, and pyodermic vegetating lesions of the hands and feet, resulting in contractures of the fingers. Routine nose and throat cultures, taken on October 6, 1948 at the hospital, were positive for C. diphtheriae, and the patient was sent to Willard Parker Hospital with a tentative diagnosis of diphtheria of the skin. Treatment at the other hospital consisted of penicillin, streptomycin, sulfapyrine, benadryl, blood transfusions and supportive therapy.

Laboratory findings revealed a trace of albumin in the urine, moderate hypoproteinemia and positive cephalin-flocculation.

*On Admission* to Willard Parker Hospital, on October 7, 1948,

the patient was apprehensive, and appeared critically and chronically ill. She had an asthmatic type of breathing. Auscultation of the chest revealed moist inspiratory and expiratory râles on the right side posteriorly. The heart sounds were rapid and weak, but no murmurs were heard. The abdomen was negative. There was a purulent discharge from the inner canthus of both eyes. The nares appeared partially obstructed with serosanguineous crusts. The mucous membranes of the mouth were mottled and had a geographic type of pigment distribution. There was hypertrophy of the gums, which also contained several blisters. Ecchymotic scars were present over the entire trunk and extremities.

*Hospital Course.* The Schick test, done on admission, was negative; cultures for diphtheria organisms of the nose, throat and skin lesions were positive on a few occasions. These cultures, however, were nonvirulent. The progress of the skin lesions was as follows: On October 13, 1948, the dressings on the patient's hands were changed while the patient was under a general anaesthetic. The old dressings were observed to be saturated with a purulent malodorous discharge. There was a general oozing of blood from the lesions after the bandages were removed. The hands were noted to have intact, clear skin on the exterior surfaces, while on the palmar surfaces, especially on the fingertips and interdigital areas, the skin appeared denuded. On October 18, 1948, and again on October 30, 1948, the dressings on the hands were changed under general anaesthesia, and each time marked improvement was noted in the lesions, so that shortly afterward physical therapy to overcome the contractures was instituted. Now regarding her pulmonary condition. Although, this patient was not dyspneic, wheezes had been heard in both hemithoraces, intermittently since admission; chest x-rays were reported as negative. On October 30, 1948, she received a general anaesthetic and the hand dressings were changed. The following afternoon the patient began to have marked dyspnea, and at times cyanosis was noted. Diminished aeration of the right lung was present with diminished excursions of the right chest wall and an expiratory grunt. Aminophylline, adrenalin and oxygen helped only slightly. On November 4, 1948, temperature spiked to 103° F., inspiratory wheezes and diminshed breath sounds on the right were heard. Bronchoscopy was performed, and a prolapse of the mucous membrane of the trachea,

acting as a pedunculated lesion and causing a partial obstruction was observed. Marked improvement in the patient's condition was noted following this procedure. However, from this time until her death about a month and a half later, she required oxygen almost continuously. An x-ray taken on November 8, 1948, revealed a patch of consolidation in the outer part of the left lower lobe. On November 23, 1948, a complete clouding of the left apex and a small infiltration in the left lower lobe was reported. No complaints were offered until December 12, 1948, when patient complained of shortness of breath. It was noted, "patient breathes like a person who has had polio involvement of the intercostals." The diaphram was mainly being used, and suprasternal retractions were noted. Bilateral wheezes were heard. Although the above findings persisted and patient continued to require oxygen, she no longer complained of shortness of breath. An x-ray on January 6, 1949, was essentially the same as that reported on November 23, 1948. Several specimens of sputum were reported as negative for acid-fast bacilli. On January 14, 1949, the patient was observed to be somewhat stuporous and confused and was moderately cyanotic. Marked inspiratory and expiratory wheezes and squeaks were heard throughout both lung fields—right lung had diminished breath sounds. Chest wall was fixed and patient seemed to be breathing with the diaphram and abdominal muscles. The abdomen was moderately distended, and the liver was 3 to 4 fingers below the costal margin. She was incontinent of urine and feces. Remainder of physical examination was essentially unchanged. She was perspiring profusely. Blood pressure was 110/60; venous pressure was not increased.

The above findings were more marked the following day and, because of the possibility of an occluded bronchitis, the ear, nose and throat consultant decided to do a bronchoscopy. There was marked spasm of the jaws, making passage for the bronchoscope extremely difficult for several minutes. The bronchoscope was finally passed and revealed a red and slightly edematous trachea. The right main bronchus was occluded by some mucous secretion which was easily aspirated. Left main bronchus was patent. No lesions of the trachea or bronchi were noted. During the bronchoscopy, respirations became less and less frequent, cyanosis became more marked and pulse was very rapid and thready. Patient failed

to respond to coramine, adrenalin and artificial respiration. It was the opinion of the ear, nose and throat consultant that there was insufficient pathology in the trachea or bronchi themselves to have caused the respiratory embarrassment.

For the first four weeks, temperature spiked to 102°-103° F., almost daily. Then the temperature leveled off around 99° F. The pulse rate, however, was elevated between 90-120.

*Autopsy Findings by Dr. Dolgopol.* The body was that of an emaciated white girl, fourteen years old. The trunk and extremities showed a spotty brownish discoloration, but the skin was smooth. The skin of the soles of the feet was scaly and desquamating. The skin of the palms was purplish and shiny. There were contractures of the fingers, the nails were absent and the nail beds were covered with epidermis. There was some desquamation of the buccal mucosa. On opening the body, the liver was found to be four cm. below the costal margin. The heart weighed 310 grams, the myocardium was firm, the mitral valve showed some thickening of the anterior cusp. The lungs were pale and fluffy, the right apex was slightly adherent to the pleura; on section several pale areas of consolidation were found in both lungs. The right bronchus contained some mucus. Other organs showed no significant changes, except the spleen which was somewhat enlarged.

Microscopic changes in the firm areas of the lungs were peculiar, the alveolar walls were tremendously thickened and consisted of young connective tissue, often mucoid in character. Outgrowths from the walls often filled the alveolar lumen. Similar outgrowths sometimes protruded into the lumen of small bronchi. The surrounding lung tissue showed moderate thickening of the alveolar walls in the proximity of the areas of the consolidation but at a distance they were fairly normal. Some of the larger bronchi in different parts of the lungs showed evidence of a rather unusual inflammatory process which often was confined to a portion of the bronchial section. This picture does not fall in any known category of pulmonary pathology. A somewhat similar picture was described by Rich in cases of diffuse fibrosis of the lungs of unknown origin. He considered that some virus could be the cause of that process. The heart was the site of an interstitial myocarditis. The interstitial infiltration consisted of loose or compact groups of mononuclear cells, which were not similar to Aschoff

nodules. The valves showed no endocarditis. The myocarditis also presented a very unusual picture and could possibly be due to the same unknown etiological factor as the pneumonia. One may speculate that some virus was the cause of both the pulmonary and cardiac pathology.

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RUBELLA DURING PREGNANCY AND CONGETINAL DEFECTS IN CHILD. (Nordisk Medicin, Stockholm, 37: 416, Feb. 27, 1948). In Zewi's 2 cases from Finland in infants whose mothers had German measles in the first and second months of pregnancy, respectively, there were bilateral congenital cataracts, with microphthalmia in one; in the other, bilateral congenital hydrophthalmus; in both, congenital heart defect. The weight at birth was low; the infants had difficulty in taking nourishment, and their physical and mental development was retarded.—*Journal A.M.A.*

CONGENITAL PORENCEPHALY IN CHILDREN. (Wiener medizinsche Wochenschrift, Vienna, 98: 184, May 1, 1948.) Stech reports a rare case of genuine porencephaly in a girl aged 4½ years. The condition was demonstrated roentgenologically in vivo and established on necropsy. After a presumably normal birth the child was given hospital treatment for debility for three months. She never learned to speak. Because of emaciation and mental deterioration the child was readmitted to the hospital. She was apathetic and subject to convulsions. Encephalography revealed a porencephalous defect in the region of the left frontotemporal-parietal lobe triangle, communicating with the lateral ventricle and with the subarachnoid space on the same side. The defect was of Guttmann's porus communicans type. Five days after the encephalography the child became lethargic, and death occurred after repeated convulsions. It is suggested that the porencephaly could have been caused by trauma to the brain during delivery. Encephalography appears to be adequate in demonstrating the lesion in doubtful cerebral disturbances.—*Journal A.M.A.*

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